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Research Article

Synthesis, characterization and anti-bacterial evaluation of metal complexes of 2-substituted quinazolin-4(3H)-one oxime derivatives

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ABSTRACT

A series of Co (II), Cu(II) and Zn (II) complexes with quinazolin-4(3H)-one oxime, 2-phenyl quinazolin-4(3H)-oneoxime, and 2-methyl quinazolin-4(3H)-oneoxime derivatives were synthesized and evaluated for antibacterial activity against both gram positive and gram negative bacteria using agar diffusion method. Among the nine derivatives, **5b** showed good potency against both strains with 10µg/ml as MIC value. Other derivatives with copper, cobalt and zinc metal complexes of quinazolin-4(3H)-oneoxime and 2-substituted quinazolin-4(3H)-oneoxime were displayed significant antibacterial activity and also less potential than **5b**.

Keywords: quinazolin-4(3H)-oxime; metal complexes; minimum inhibitory concentration; anti-bacterial activity

INTRODUCTION

Quinazolin-4(3H)-one oximes are heterocyclic fused ring systems and are moieties of considerable interest because of the diverse range of their biological properties like anticancer, anti-inflammatory, anticonvulsant, anti hypertensive and antimicrobial activities (Desai et al., 2006). Considering, the importance of transition metal complexes as active moieties in antibacterial, antitubercular and antileprotic, antiviral and antimalarial activities. Novel oxovanadium complexes with 2-methyl-3-(pyridine-2-ylmethyleneamino)quinazolin-4(3H)-ones were reported as antimicrobial agents by Prasad et al., 2011. Quinazoline-4-one and 8-hydroxyquinoline derivatives were evaluated for antifungal activity and reported by Vashi et al., 2009. In the present paper synthesis, characterization and antibacterial activities of Co (II), Cu(II) and Zn (II) complexes with quinazolin-4(3H)-oneoxime, 2-phenyl quinazolin-4(3H)-oneoxime, and 2-methyl quinazolin-4(3H)-oneoxime were reported.

MATERIALS AND METHODS

All the solvents used were of analytical grade. Anthranilic acid, formamide, acetamide, benzamide and metal salts were procured from Merck, Himedia and Sd-fine respectively. The synthesized compounds were identified and characterization by spectral studies. Melting points were determined in an open capillary. All the compounds were tested for their antibacterial activity gram positive bacterial like Coryne bacterium, B. subtilis and Gram negative bacteria like E. coli, Proteus vulgaris at the concentration of 50, 100, 150, 250, 500 and 1000µg using cup plate method.

General method for the synthesis of qinazolin-4(3H)-oneoxime (5a-5i) (Kuwar et al., 2006)

Step 1: Synthesis of 2-substituted quinazolin-4(3H)-one (1-3)

7.3 mmoles of anthranilic acid was air condensed with excess of amide (36.5 mmoles) at 120-130^{0}C for 4-5hrs, and recrystallized the resultant product with ethanol.

Step 2: Synthesis of 2-substituted quinazolin-4(3H)-one oxime (4a-4c): (Kuwar et al., 2006)

A solution of hydroxylamine hydrochloride (0.05m) and sodium hydroxide (0.05m) in 25ml of aqueous methanol added to a boiling solution of step-1 product 0.05m, which was dissolved in 25ml of methanol. Refluxed the mixture for 2hr and allowed to crystallize the product obtained. Completion of the reaction was monitored by TLC using the solvent phase ethyl acetate and petroleum ether (5:5). Product was recrystallized from ethanol.

Step 3: Synthesis of metal complexes of 2-substitutedquinazoli-4(3H)-one oxime (5a-5i).

0.002mole of step-2 product was dissolved in 40ml of ethanol, to this 0.001mole of 25ml of aqueous metal salt added drop wise, stirred the mixture for 30 min filtered the precipitated product and washed with water and ethanol.

The synthesized compounds were characterized by IR, ^{1}HNMR, and Mass spectroscopy.

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Table 1: The MIC values of synthesized compounds (5a-5i)

Compound	R	M	% Yield	MIC (µg/mL)			
				P. vulgaris	E. coli	C. diphtheria	B. subtilis
5a	H	Zn	65	100	150	100	250
5b	H	Co	69	10	10	10	10
5c	H	Cu	67	50	150	250	100
5d	CH_3	Zn	71	250	500	100	100
5e	CH_3	Co	73	750	500	100	250
5f	CH_3	Cu	69	500	150	150	250
5g	Ph	Zn	67	500	150	75	500
5h	Ph	Co	66	100	150	100	150
5i	Ph	Cu	73	250	100	100	100

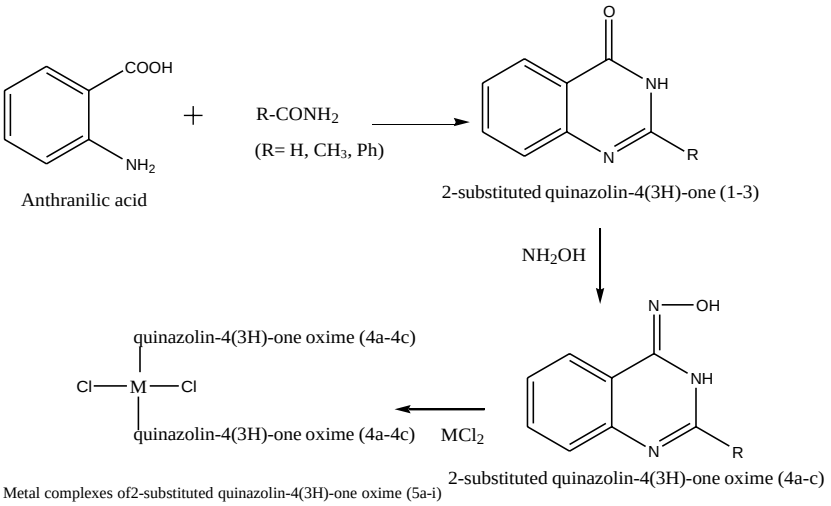

Figure 1: General method for the synthesis of metal salts of qinazolin-4(3H)-oneoxime (5a-5i)

Quinazolin-4(3H)-one oxime (4a): Anthranilic acid treated with excess of formamide and proceeded as discussed in general method. IR (KBr, υ in cm^{-1}): 3526 (O-H str in oxime), 1652 (C=N str in oxime). **^{1}HNMR (400MHz, $CDCl_3$, δ in ppm):** 5.2 (br s, 1H, NH at 3rd position), 7.1-7.6 (m, 5H, aromatic ring), 11.2 (br s, 1H, O-H group in =N-OH). **APCI-MS:** m/z = 161 M^+.

2-Methyl quinazolin-4(3H)-one oxime (4b): Anthranilic acid treated with excess of acetamide and proceeded as discussed in general method. IR (KBr, υ in cm^{-1}): 3542 (O-H str in oxime), 1658 (C=N str in oxime). **^{1}HNMR (400MHz, $CDCl_3$, δ in ppm):** 1.2 (s, 3H, 2-CH_3), 5.09-5.18 (br s, 1H, NH at 3rd position), 7.05-7.76 (m, 4H, aromatic ring), 11.25-1134 (br s, 1H, O-H group in =N-OH). **APCI-MS:** m/z = 175 M^+.

2-Phenyl quinazolin-4(3H)-one oxime (4c): Anthranilic acid treated with excess of benzamide and preceded as discussed in general method. IR (KBr, υ in cm^{-1}): 3548 (O-H str in oxime), 1654 (C=N str in oxime). **^{1}HNMR (400MHz, $CDCl_3$, δ in ppm):** 5.11-5.23 (br s, 1H, NH at 3rd position), 7.06-7.85 (m, 9H, aromatic ring), 11.25-1134 (br s, 1H, O-H group in =N-OH). **APCI-MS:** m/z = 237 M^+.

Evaluation of in-vitro anti-bacterial activity

The in-vitro Antibacterial activity was performed by Agar diffusion method. The synthesized metal complexes (5a-5i) were evaluated for *in vitro* antibacterial activity against Gram-positive bacteria like Bacillus Subtilis, Coreny bacterium, and Gram Negative bacteria like Escherichia Coli, Proteus Vulgaris. Microbial cultures are prepared and are kept in slant position allowed to cool. Cultures (procured from Sri Venkateshwara University, Tirupati, India) are used as seed for fresh culture, in aseptic cabinet each selected micro organism was transferred into the fresh cultured test tube by inoculating loop. These test tubes were incubated for 24 - 48hrs growth was observed, from this sub culture was prepared. When the temperature of the agar media was 45^0C, subculture was added and poured into the Petri plates allowed to solidify. Wells are made in the Petri plates. In aseptic cabinet Standard Drug and Different concentration of sample prepared was poured into the wells of Petri plates by micro pipette. These Petri plates were kept in an incubator for 24hrs, zone of inhibition was observed (S Irshad et al., 2012).

RESULTS AND DISCUSSION

Synthesis of metal chloride complexes of quinazolin-4(3H)-oneoxime was carried out via Niemantowski reaction followed by oxime formation, which in turn react with metal chlorides like zinc chloride, cobalt chloride or copper chloride in 2:1 ratio. Spectral data of 2-substituted quinazolin-4(3H)-oneoximes (4a-4c) were

conformed the respective structures. The IR spectra of the title compounds showed a broad band at 3500-3600cm^{-1} assignable to oxime functional group and a strong band at 3420-3400cm^{-1} indicating secondary amine functional group. The ^{1}H NMR spectrum of the compounds supported the structures of the compounds 4a-4c. These compounds showed a broad singlet at 5.1-5.4 ppm indicating –NH proton in quinazolinyl ring, a multiplet 6.6-7.4 ppm representing aromatic protons and a broad singlet 11.2-12.5 ppm due to the oxime proton. Compounds 5a-5i showed a molecular ion peak at their respective molecular weight.

All the synthesized compounds were screened for their in-vitro antibacterial activity against gram positive and gram negative bacteria, namely Bacillus subtilis, Coryne bacterium diphtheria, and E. coli, Proteus vulgaris respectively, by the agar diffusion method using Tetracycline and Erythromycin as reference standard drugs respectively. The results were tabulated in the Table 1. All the synthesized nine derivatives (5a-5i) were exhibited the significant antibacterial activity. Of these derivatives, compound 5b displayed good activity, may be due to the cobalt complexes. Compound 5c existing as copper chloride complexes of quinazoline-4(3H)-oneoxime showed second promising activity. The other derivatives 5d-5f showed less potency of all the derivatives that may be due to their methyl substitution at 2nd position whereas, derivatives 5g-5i were intermediatory in antibacterial activity because of the phenyl substitution at 2nd position.

CONCLUSION

Here, we reported simple and feasible procedure for the title compounds. All the synthesized derivatives were screened for antibacterial activity. Among them **5b** showed good potency against both strains with 10µg/ml as MIC value which may be due to cobalt(II)chloride complexes of quinazoli-4(3H)-one oxime than other metal salts like copper and zinc.

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